Spinal Muscular Atrophy:
From mouse model to potential drug treatment

Hung Li, Ph.D.
Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan.

Email: hungli@ccvax.sinica.edu.tw

Homozygous mutation of the telomeric SMN (*SMN1*) gene in humans is associated with proximal spinal muscular atrophy (SMA), a severe motor neuron disease leading to muscle weakness with an onset predominantly in infancy and childhood. To further understand the functional role of the SMN gene in SMA, we produced mouse lines carrying a knockout mutation of the mouse Smn gene and transgenic mouse lines that expressed the human centromeric SMN (*SMN2*) gene. Mice with the homozygous *Smn* knockout mutation died during the peri-implantation stage. Transgenic mice harboring the human *SMN2* with the Smn gene knockout showed pathological changes in spinal cord and skeletal muscle similar to SMA patients. The severity of the pathology in the knockout-transgenic mice is correlated with the amount of intact SMN protein. The knockout-transgenic mice clearly demonstrate that the *SMN1* gene is responsible for SMA and should be useful in elucidating the molecular mechanisms of the *SMN* gene and in the design of therapeutic protocols for SMA patients.

As a first step toward designing a therapeutic protocol for SMA patients, we used *SMN2*-transfected mouse motor neuron cell line to screen a series of drugs for their possible effect on the expression of the *SMN2* gene. The effective drug was then used to treat the SMA-like mice to explore the possible treatment potential for human SMA patients. We will present one of the compounds that can effectively increase the amount of intact SMN protein from *SMN2* gene both *in vitro* and *in vivo*. These results suggest that this compound may be an effective drug for the treatment of human SMA patients.